

Section 7.3 Preliminary Results

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1 Assumptions

- The protein production starts in the log phase of bacterial growth.
- The switch that stops the bacterial growth takes a small time t_s .
- The amount of quorum sensing molecule (A) at time $t = 0$ is 0.

2 Notations

- A – Amount of quorum sensing molecule
- A_t – Threshold amount of quorum sensing molecule (Adjustable parameter, by changing affinity of quorum sensing molecule for the switch)
- n_i – Initial number of bacteria in solution
- n_f – Final number of bacteria in solution (at threshold)
- r – Rate of production of quorum sensing molecule per bacteria (Adjustable by changing promoter)
- g – Inverse of generation time

3 Calculation

Since the bacterial is in the log phase, the number of bacteria at time $t = t$, if the initial number of bacteria was n_i is,

$$n = n_i 2^{gt}$$

So, the rate of production of the quorum sensing molecule, if the rate of production by each bacteria is r is,

$$\frac{dA}{dt} = rn_i 2^{gt}$$

Now, if we solve it,

$$dA = rn_i 2^{gt} dt$$

Integrating,

$$\begin{aligned} A &= \frac{rn_i 2^{gt}}{g} \\ \Rightarrow A_t &= \frac{rn_i 2^{gt}}{g} = \frac{rn_f}{g} \\ \Rightarrow n_f &= \frac{A_t g}{r} \end{aligned}$$

Now, expressing n_f in terms of n_i , and taking the time to reach threshold is t^* ,

$$\begin{aligned} n_i 2^{gt^*} &= \frac{A_t g}{r} \\ \Rightarrow t^* &= \frac{1}{g} \log_2 \frac{A_t g}{rn_i} \end{aligned}$$

If we modify our equation slightly to incorporate the fact that production at $t = 0$ is 0, we get,

$$\begin{aligned} A(t, n_i) &= \frac{rn_i}{g} (2^{gt} - 1) \\ \Rightarrow t^* &= \frac{1}{g} \log_2 \left(\frac{A_t g}{rn_i} + 1 \right) \end{aligned}$$

Considering the fact that the switch takes time t_s to work,

$$\begin{aligned} A(t^* + t_s, n_i) &= \frac{rn_i}{g} (2^{g(t^* + t_s)} - 1) \\ &= \frac{rn_f 2^{gt_s}}{g} - \frac{rn_i}{g} \text{ (because } n_f = n_i 2^{gt^*} \text{)} \end{aligned}$$

The cell density after the switch turns on is n'_f . So,

$$\begin{aligned} n'_f &= n_i 2^{g(t^* + t_s)} \\ &= n_f 2^{gt_s} \\ &= \left(\frac{A_t g}{r} + n_i \right) 2^{gt_s} \end{aligned}$$

To achieve initial density, n_i again, the fraction to be removed is,

$$\frac{n'_f - n_i}{n'_f} = \frac{\frac{A_t g}{r}}{\frac{A_t g}{r} + n_i} + \frac{n_i (2^{gt_s} - 1)}{\left(\frac{A_t g}{r} + n_i \right) 2^{gt_s}}$$

Let us assume the cells secrete product for t_p amount of time after the switch is turned on. The constraint on t_p and t^* is that their sum is a constant for a given amount of media, since it basically represents the nutrient content. So, $t_p = C - t^*$, where C is the constant. Let us assume that the product is produced at a per-capita rate, p . So, total product is,

$$P = pt_p n'_f$$

Product formed per unit total time (one cycle time) is,

$$B = \frac{P}{t^* + t_s + t_p}$$

Assuming t_s is a constant (given a robust switch), the denominator is a constant. Thus to maximize product formed per unit total time (one cycle time), we just maximize its numerator P .

$$P = p \left(\frac{A_t g}{r} + n_i \right) 2^{gt_s} \left(C - \frac{1}{g} \log_2 \left(\frac{A_t g}{r n_i} + 1 \right) \right)$$

Defining $\frac{A_t}{r} = k$, (please note that A_t and r are adjustable) we can write P in terms of k , and take its derivative with respect to k .

$$\frac{dP}{dk} = p 2^{gt_s} \left(gC - \log_2 \left(\frac{k g}{n_i} + 1 \right) - \frac{1}{\ln 2} \right)$$

When B is maximum, $\frac{dP}{dk} = 0$. Using this result, we derive the optimal k (for highest B),

$$k^* = \left(2^{(gC - \frac{1}{\ln 2})} - 1 \right) \frac{n_i}{g}$$

k^* makes biological sense only if $gC > \frac{1}{\ln 2}$, otherwise $k^* < 0$. but gC is the number of generations of division and secretion which is expected to be much greater than ≈ 1.5 ($\frac{1}{\ln 2}$).

At k^* , $\frac{dP}{dk} = 0$, but this is insufficient to say that k^* is a maxima of B (just a critical point is proved). However, since there is only one critical point, and $\frac{dP}{dk}$ at k^* , when $k^* > 0$ is also positive, it implies that B increases from $k = 0$ and k^* has to be a maxima. Thus we have shown that this quorum sensing system can provide optimal yield by tuning the parameters. Important parameters like yield, removal fraction and final density could also be calculated for the system.